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Low free testosterone is associated with increased mortality in frail surgical patients

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ABSTRACT

Background: Preoperative frailty has been associated with adverse postoperative outcomes. Additionally, low testosterone has been associated with physical frailty and cognitive decline. However, the impact of simultaneous frailty and low testosterone on surgical outcomes is understudied.
Methods: Preoperative frailty status and testosterone levels were obtained in patients undergoing a diverse range of surgical procedures. Preoperative frailty was evaluated independently and in combination with testosterone through the creation of composite risk groups. Relationships between preoperative frailty and composite risk groups with overall survival were determined using Kaplan–Meier and logistic regression analyses. Bivariate analysis was used to determine the associations between frailty and testosterone status on postoperative complications, length of hospital stay, and readmission rates.
Results: Median age of the cohort was 63 years, and the median follow-up time was 105 weeks. Thirty-one patients (23%) were frail, and 36 (27%) had low free testosterone. Bivariate analysis demonstrated a statistically significant relationship between preoperative frailty and overall survival ($P = .044$). In multivariate analysis, coexisting frailty and low free testosterone were significantly associated with decreased overall survival (hazard ratio 4.93, 95% confidence interval, 1.68–14.46, $P = .004$).
Conclusion: We observed preoperative frailty, both independently and in combination with low free testosterone levels, to be significantly associated with decreased overall survival across various surgical procedures. Personalizing the surgical risk assessment through the incorporation of preoperative frailty and testosterone status may serve to improve the prognostication of patients undergoing major surgery.

INTRODUCTION

Initially defined by Fried et al as an age-related decline in physical function and emotional reserve, frailty is a multifactorial process that is associated with increased morbidity and mortality in patients managed with surgery [1,2]. Hence, frailty has gained attention as a preoperative screening tool, as it may outperform traditional screening measures such as the Eastern Cooperative Oncology Group (ECOG) and American Society of Anesthesiologists (ASA) scores [1,3,4]. In previous studies, combining frailty with other patient-specific factors, such as cognitive function and comorbidities, has demonstrated value in predicting long-term survival outcomes, surgical complications, and length of hospital stay [1,5,6]. As a patient's frailty status may offer an objective view into his or her ability to tolerate surgery, it is important to clarify the relationship between frailty and postoperative outcomes [1].

Testosterone (T) is an essential hormone involved in the maintenance of physiologic homeostasis and, when deficient, can contribute to decreased muscle strength, bone differentiation, erythropoiesis, and cognitive function [7,8]. The majority of serum T is bound to plasma protein, with 50%–60% bound to sex hormone-binding globulin and 40%–

Abbreviations: T, testosterone; OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG, Eastern COoperative Oncology Group; ASA, American Society of Anesthesiologists; CCI, Charlson Comorbidity Index; eGFR, estimated Glomerular Filtration Rate; BMI, body mass index; IQR, interquartile range.

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50% bound to albumin, with the remaining 1–2% circulating freely. Collectively, free and albumin-bound T represents the bioactive form [9]. It is well established that androgen levels decline steadily with age, with studies suggesting a potential interplay between T deficiency and frailty [12,13]. However, to our knowledge, no studies have investigated the prognostic utility of combined frailty and T status in patients undergoing major surgery.

We hypothesize that preoperative physical frailty will be associated with T deficiency in male surgical candidates. In addition, we hypothesize that physical frailty, when analyzed independently and in combination with low free T, will be significantly associated with adverse outcomes in patients undergoing major surgery.

MATERIALS AND METHODS

Study Population. The Emory Institutional Review Board approved this prospective study of patients undergoing major surgery at Emory University Hospital (IRB No. 55598). Informed consent was obtained during the preoperative visit. Patients under the care of three urologists were screened before their preoperative visit for evaluation of inclusion and exclusion criteria. A strobe diagram displaying the enrollment and exclusion process is shown in Supplemental Fig 1. Inclusion criteria consisted of adult male patients who were scheduled for urologic surgical procedures requiring overnight hospital admission, including partial and radical nephrectomy, prostatectomy, cystectomy, adrenalectomy, and penectomy. Seventeen patients from our previous prospective studies who underwent general surgery, thoracic surgery, or surgical oncology intervention requiring hospitalization and had valid preoperative T values were also included for analysis [6].

Patients with history or plans to undergo procedures impacting T levels, such as orchiectomy, or with a history of T altering treatment, such as prior history of chemotherapy, radiation, androgen deprivation therapy, and medication such as T supplements, were excluded. Patients who failed to obtain valid T measurements, were unable to ambulate, had poor dexterity, or had an inability to perform the grip strength tests were excluded from this study (Supplemental Fig 1).

An a priori power analysis was conducted pre-enrollment to determine the appropriate sample size for this study. A sample size of 130 individuals, with a 3:1 ratio of nonfrail to frail patients, was determined to have 80% power for detecting a 30% difference in free T at an α of .05.

Testosterone and Frailty Measurements. T levels have been shown to decline in the afternoon due to diurnal variation, which also decrease with age [10]. As a result, free and total T levels were obtained during the preoperative visit between 8:00 AM and noon as recommended by the Endocrine Society [11]. Total T was measured by immunoassay, and free T was measured by liquid chromatography tandem mass spectrometry (Quest Diagnostics, Secaucus, NJ). Both were calibrated against the Centers for Disease Control and Prevention laboratory values as part of the Hormone Standardization Project. Total and free T levels were assessed as normal or low based on the reference ranges provided by the Endocrine Society and Quest Diagnostics (Appendix A).

Patients were assessed for frailty from 5 categories: grip strength, walking speed, shrinking, exhaustion, and low physical activity (Appendix B) [1]. Grip strength of the dominant hand was tested using a hydraulic hand dynamometer (JAMAR Sammons Preston, Bolingbrook, IL). The test was repeated 3 times, and the mean grip strength result was calculated. Each category yielded a dichotomous score of 0 or 1, and the sum of all 5 categories yielded the total score. Following previous protocols, we combined the prefail (score = 2) with the frail group because of small sample size of frail patients ($n < 10$) [2,6]. Patients with total scores of 0 or 1 were classified as nonfrail, and patients with total scores of 2 to 5 were classified as frail. A 4-level system that combined frailty and age-adjusted free T was developed to further classify patients into one of the following 4 groups: nonfrail with normal free T, nonfrail with low free T, frail with normal free T, and frail with low free T.

Preoperative Covariates. Demographic information including age at time of surgery, sex, race/ethnicity, and body mass index (BMI) were obtained during the preoperative consultation. Additionally, patients were assessed for risk indices, including ASA score, Charlson Comorbidity Index (CCI), and ECOG score [3,12,13]. Serum biochemical measurements (hemoglobin, creatinine, estimated glomerular filtration rate [eGFR], platelets) were also obtained preoperatively and assessed as normal or low based on the reference ranges provided by the Emory Laboratory (Appendix A).

Primary and Secondary Outcomes. The primary outcome of this study was *overall survival* (OS), defined as the time from surgery to death from any cause. Secondary outcomes included postoperative length of stay, discharge disposition (home versus facility), as well as postoperative major complications and hospital readmissions within 30 and 90 days. Complications were assessed using the Clavien–Dindo classification system, with major complications defined as a Grade ≥ IIIb [14]. Complications with a grade < IIIb were not included in the analysis. Mortality data were acquired through a combination of follow-up phone calls, medical record review, and the Social Security National Death Index.

Statistical Analysis. Descriptive statistics for each variable were reported for the overall population. Bivariate analyses between demographic, clinical, and outcome variables with each composite free T and frailty cohort were reported. Free T levels and frailty scores were tested with all demographic and outcome variables individually. Bivariate associates of categorical outcomes or cohorts were performed using the χ^2 or Fisher exact test for categorical covariates and ANOVA for numerical covariates.

Multivariate models were created for outcome variables through logistic regression and a Cox proportional hazard model for overall survival while controlling for age, race, sex, BMI, CCI score, ECOG score, and ASA score. The multiple logistic regression model was built with backward stepwise elimination at α level of .3. All variables were initially included in the multivariate model and were consecutively removed with the largest P value > .3. This was continued one at a time until all variables in the model had a P value < .3. Kaplan–Meier plots were created to evaluate the associations between the composite free T and frailty cohorts and OS. All statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Demographics. The study included 136 male patients undergoing surgery between 2014 and 2019 at our tertiary care academic medical center. Patient demographics, including the preoperative frailty and laboratory characteristics of our cohort, are presented in Table 1. Sixty-six percent of the cohort were white, the median age at time of surgery was 63 years (interquartile range [IQR] 54–70), and the median BMI of our cohort was 28.8 (IQR 26.4–32.8) kg/m^2. The majority of surgeries performed were urological procedures (87.5%). Other surgery divisions included cardiac (3.68%), general surgery (2.21%), neurosurgery (4.41%), thoracic (1.47%), and vascular (0.74%). Among all surgeries, 54 (39.7%) were open procedures, 43 (31.6%) were robotic, and 28 (20.6%) were laparoscopic. Surgeries were classified as oncologic versus non-oncologic procedures, with 118 (86.6%) being oncologic surgeries and 18 (13.4%) non-oncologic surgeries. Patients were not compared by detailed surgical techniques due to high heterogeneity.

Traditional preoperative risk screening revealed that nearly 75% of our cohort had an ASA score of 3 or 4 (74.3%), whereas nearly 71% had an ECOG score of 0. The median CCI score was 2 (IQR 0–4) (Table 1).

Table 1
Demographic and clinical data

Variable	*Total population* (n = *136*)	P *value with combined frailty & T score*
Age at time of surgery, median (IQR)	63 (54–70)	.009
Race, *n (%)*		.892
White	90 (66.2)	
Nonwhite	46 (33.8)	
BMI (kg/m^2), median (IQR)	28.8 (26.4–32.8)	.077
Date of surgery, *n (%)*		.282
2014–2016	37 (27.2)	
2017–2019	99 (72.8)	
Surgery technique, *n (%)*		.329
Open	54 (39.7)	
Robotic	43 (31.6)	
Laparoscopic	28 (20.6)	
Other	11 (8.09)	
Primary surgeon division, *n (%)*		.819
Urology	119 (87.5)	
Other	17 (12.5)	
Surgery types, *n (%)*		
Oncology	118 (86.6)	.510
Non-oncology	18 (13.4)	
ASA, *n (%)*		.116
1–2	35 (25.7)	
3–4	101 (74.3)	
CCI, *n (%)*		.070
0	61 (44.9)	
1–2	14 (10.3)	
≥3	61 (44.9)	
ECOG, *n (%)*		.174
0	96 (70.6)	
1–2	40 (29.4)	
Hemoglobin (g/dL)		
Patients with abnormal levels, *n (%)*	55 (40.4)	.022
Creatinine (mg/dL)		
Patients with abnormal levels, *n (%)*	35 (25.7)	.430
GFR (mL/min/1.73 m^2)		
Patients with abnormal levels, *n (%)*	38 (27.9)	.661
Platelets (10E3/μL)		
Patients with abnormal levels, *n (%)*	21 (15.4)	.065
Free testosterone (pg/mL), median (IQR)	43.1 (32.5–55.3)	–
Normal free T, *n (%)*	100 (73.5)	
Low free T, *n (%)*	36 (26.5)	
Total testosterone (ng/dL), median (IQR)	261 (207–346)	–
Normal total T, *n (%)*	54 (39.7)	
Low total T, *n (%)*	82 (60.3)	
Low free T and low total T, *n (%)*	31 (22.8)	
Frailty score, *n (%)*		–
0	70 (51.5)	
1	35 (25.7)	
2	22 (16.2)	
3	7 (5.2)	
4	1 (0.7)	
5	1 (0.7)	
Frailty, *n (%)*		–
Nonfrail (score 0–1)	105 (77.2)	
Frail (score 2–5)	31 (22.8)	

Independent Analysis of Frailty, Testosterone, and Other Serum Studies. After adjusting for age, 36 patients (26.5%) had low free T and 82 (60.3%) had low total T (Table 1). Among them, 31 (22.8%) patients had both low free T and low total T values. The Fried criteria assessment revealed that 31 (22.8%) patients were deemed frail with a frailty score ≥ 2. Free T was associated with physical frailty, as determined by bivariate analysis ($P < .001$, Table 2). There was no significant association found between total T and physical frailty ($P > .05$).

Table 2
Bivariate analysis of free testosterone with frailty

	Free T levels, n *(%)*		P *value*
Categories of frailty, *n (%)*	Normal free T	Low free T	<.001
Nonfrail (score 0–1)	84 (61.8)	21 (15.4)	
Frail (score 2–5)	15 (11.0)	16 (11.8)	

In bivariate analysis, hemoglobin and platelet levels were significantly associated with physical frailty ($P = .03$ and $P = .02$, respectively). Except for levels of hemoglobin ($P = .02$, Table 1), other biochemical measurements did not have a statistically significant association with the combined frailty and free T score. The relationship between serum T and BMI was examined, and the association was not statistically significant ($P = .3$). The same was found for the association between BMI and the composite frailty and free T score ($P = .08$). No other serum laboratory measurements were found to be associated with free T (all $P > .05$).

Composite System and Surgical Outcomes. Eighty-four (61.8%) patients were classified as nonfrail with normal levels of free T, 21 (15.4%) patients were nonfrail but had low levels of free T, 15 (11.0%) patients were frail with normal free T, and 16 (11.8%) patients were both frail and had low free T (Table 2).

In total, 22 deaths occurred (16.2%) over the median follow-up period of 105 weeks. Two of the 22 deaths occurred within 30 days after surgery, and 1 additional death occurred within 90 days after surgery. Causes of death for these 3 patients included progression of disease (1), multiorgan failure (1), and cardiac arrest (1). Among all deaths, 3 were of unknown causes, 6 were disease-related or due to disease progression, and the rest ($n = 13$) were due to pneumonia, hemorrhagic stroke, heart failure, liver failure, sepsis, or multiorgan failure.

In the bivariate analysis, both low free T ($P = .005$) and frailty ($P = .015$) were independently associated with 1-year mortality. Similarly, the composite free T and frailty score was significantly associated with 1-year ($P = .003$) and 2-year ($P = .028$) mortality.

Other postoperative outcomes, including 30- or 90-day mortality, presence of major complications, 30- or 90-day readmission, length of stay, and discharge disposition, were not significantly associated with frailty, free T, or the composite score.

Composite System and Overall Survival. Surgical technique, categorical eGFR levels, and the composite frailty and T score were found to have *P* values < .3 with OS in univariate analysis. Kaplan–Meier analysis of the 4-level composite system combining frailty and free T revealed significant differences in OS between groups (log rank $P = .019$, Fig 1). Among the 4 groups, frail patients with low free T had the shortest OS when compared to the reference group. In multivariate analysis, presence of frailty and low free T was significantly associated with decreased overall survival (hazard ratio [HR] 4.93, 95% confidence interval [CI] 1.68–14.46, $P = .004$; Table 3). Although not found to be significant, nonfrail patients with low levels of free T were also at risk, with a higher risk of mortality compared to the reference group (HR 2.11, 95% CI 0.70–6.37, $P = .185$).

DISCUSSION

In this prospective study, we evaluated the combined effect of free T levels and physical frailty in predicting postoperative outcomes across various surgical procedures. We found frailty and free T to be independent predictors of 1-year mortality. Moreover, we found that the combination of frailty and free T was more significantly associated with 1-year mortality than frailty alone (HR 4.93, 95% CI 1.68–14.46, $P = .004$ vs HR 1.82, 95% CI 0.39–8.51, $P = .45$).

T plays an important role in many physiologic and metabolic pathways, and metabolic syndrome and T deficiency demonstrate a bidirectional causal relationship. In male subjects, T is converted to estradiol by aromatase in the adipose tissue. Increased fat deposition leads to an increased conversion of T to estradiol, which in turn inhibits central gonadotrophin secretion through a negative feedback mechanism [15,16]. The resulting T deficiency contributes to

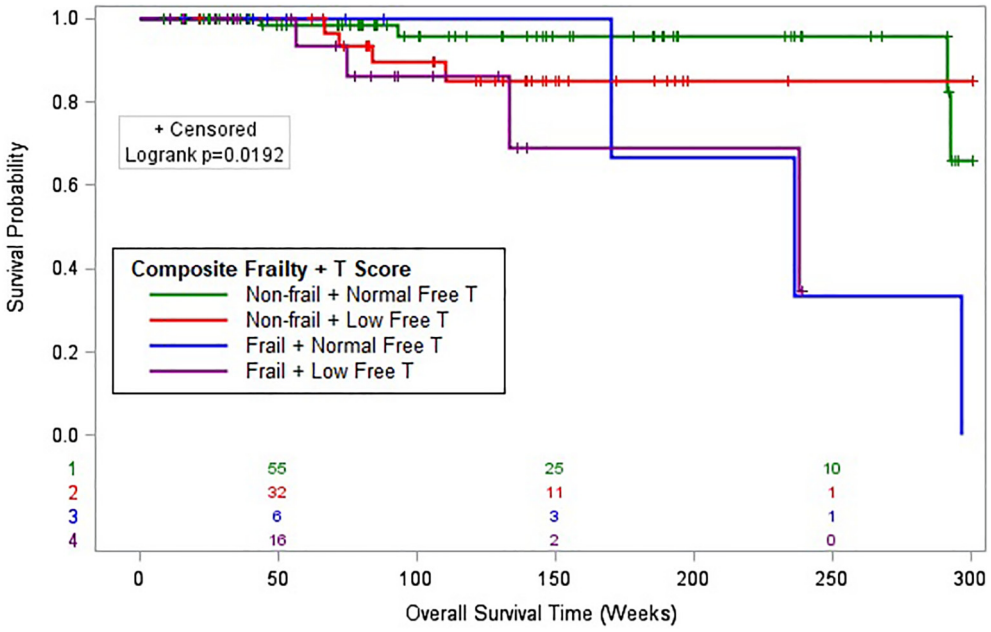

Fig 1. Kaplan–Meier curve displays the overall survival of patients following major procedures in all four levels of the composite system with frailty score and free testosterone (T) level combined ($n = 136$). The log-rank test indicates a significant difference between the survival curves.

decreased insulin sensitivity and metabolic inflexibility between catabolic and anabolic states, which disrupt normal muscle metabolism and in turn cause reduced lean muscle mass [16]. T is important for stimulating bone formation and muscle strength, whereas T deficiency is associated with decreased bone mineral density, muscle wasting, and cognitive impairment [7,8,17]. T deficiency affects multiple aspects of physical and mental health, leading to the frailty phenotype. Moreover, metabolic imbalance and hypogonadism may introduce comorbidities such as diabetes and cardiovascular disease. These factors combined may lead to increased risks of surgical complications, prolonged recovery periods, and mortality.

There is a paucity of literature delineating the influence of serum T levels on surgical outcomes. One retrospective study suggests that low T level at time of kidney transplant is associated with increased mortality and graft loss, notably with a higher rate of mortality secondary to cardiovascular and septic events [18]. Here, we observed low preoperative T levels to be significantly associated with decreased mortality in several surgical procedures. Furthermore, 26.5% of our cohort had low preoperative free T levels. Given this relatively high prevalence and the observed association between low free T and postoperative mortality, further research is needed to investigate the utility of analyzing T in the preoperative risk assessment.

Current interventions to combat the frailty phenotype involve physical exercise, nutritional supplements, cognitive training, or a combination of these methods [26,27]. Frail patients participating in physical exercise show a greater increase in functional ability and fewer surgical complications when compared to control groups [19,20]. Meanwhile, nutritional intervention shows a large degree of variation in its effect on modifying frailty status. Some studies suggest improvements in malnourished patients, whereas other studies have found no significant improvements, after nutritional intervention [21]. A randomized trial comparing the effectiveness of physical exercise, nutritional

Table 3
Univariate and multivariable analysis of preoperative variables with overall survival (months)

	Univariate analysis		*Multivariable analysis*	
Variable	*HR (95% CI)*	*P value*	*HR (95% CI)*	P *value*
Frailty & free T score		.019		.037
[1] Nonfrail + normal free T	–	–	–	–
[2] Nonfrail + low free T	2.30 (0.77–6.88)	.136	2.11 (0.70–6.37)	.185
[3] Frail + normal free T	1.71 (0.37–7.95)	.497	1.82 (0.39–8.51)	.449
[4] Frail + low free T	5.52 (1.89–16.12)	.002	4.93 (1.68–14.46)	.004
Age (0 to 65 vs > 65)	1.30 (0.56–3.03)	.542		
Race (white versus nonwhite)	1.02 (0.41–2.50)	.973		
BMI	0.95 (0.88–1.04)	.262		
Date of surgery (2014–2016 vs 2017–2019)	1.39 (0.49–3.93)	.531		
Surgery technique (robotic versus other)	2.63 (0.77–8.94)	.121	2.32 (0.68–7.95)	.182
Primary surgery division (urology versus other)	0.66 (0.24–1.82)	.421		
ASA (1–2 vs 3–4)	1.09 (0.40–2.98)	.862		
CCI (0–2 vs ≥ 3)	1.46 (0.63–3.37)	.381		
ECOG (0 vs 1–2)	1.27 (0.54–3.00)	.591		
Hemoglobin (patients with normal versus abnormal levels)	1.46 (0.63–3.40)	.376		
Creatinine (patients with normal versus abnormal levels)	1.48 (0.60–3.64)	.392		
GFR (patients with normal versus abnormal levels)	1.68 (0.70–4.00)	.244	1.67 (0.69–4.05)	.261
Platelets (patients with normal versus abnormal levels)	1.39 (0.47–4.12)	.558		

supplements, cognitive training, and a combination of the 3 methods demonstrates a similar level of improvement in frailty status for each intervention group [22]. Given the correlation between low T and frailty, T replacement therapy (TRT) has theoretical potential for managing frailty. Currently, a diagnosis of sexual dysfunction or hypogonadism is an indication for TRT. Meanwhile, the use of TRT in late-onset hypogandism is still under debate, as there have been mixed results on whether TRT results in increased cardiovascular risks, and other uses of TRT outside of the indications mentioned above are to be evaluated on a case-to-base basis [23–25]. Benefits of TRT include increased lean body mass, increased bone density, increased hemoglobin levels, improved physical function, and improved mood [26]. Therefore, T supplementation may improve physical functioning and energy levels in frail patients; however, future studies are warranted to investigate the risks and benefits of TRT in this scenario [27].

In our study, most of the deaths occurred outside of the 90-day postoperative period, indicating that surgery may not influence perioperative mortality rates among patients with frailty and low free T. Even if surgery was not a strong contributing factor in the immediate postoperative period, it is still important for surgeons to be cognizant of frailty's potential long-term effects on survival [28]. In the current study, we demonstrated frailty and low free T to be significantly associated with inferior survival outcomes beyond the perioperative period. We also observed that 50% of deaths occurred after 2 years and most were not disease-specific. This may be secondary to the high comorbidity rate in our cohort, as nearly 45% of our patients had a CCI ≥ 3. Higher CCI scores impart increased mortality rates in patients undergoing major surgery, offering a potential rationale for the high percentage of deaths attributed to causes unrelated to their surgically managed pathology [29].

This study is limited by several factors. During screening, a large number of patients were excluded owing to history of medical or surgical treatments that would interfere with T results. This included prior history of chemotherapy, radiation, androgen deprivation therapy, and medication such as T supplements. Additionally, we had a high percentage of exclusion cases due to a large number of invalid or missed T results. This leads to a relatively small sample size and a short follow-up period that could limit the power of our analyses. Our cohort was recruited at a single tertiary medical center, with majority being evaluated for suspected or known neoplasm. Therefore, there may be selection bias, thus limiting the external validity and generalizability of our conclusions to the general population. Furthermore, patients unable to finish the physical frailty assessment due to ambulatory problems or other ailments were excluded, and results may not be applicable in populations with further physical impairment. This study also examined T only once, which is distinct from other studies and guidelines, and therefore is unable to capture the changes of T levels [11]. Additionally, we did not include other hormone measurements, such as luteinizing hormone, albumin, or sex-hormone binding globulin, which may contribute to related physiological processes [30]. Lastly, this is an observational study with no interventions; therefore, we cannot confirm causal relationships between T, frailty, and survival outcomes. Further multicenter prospective trials are warranted to confirm the results.

In conclusion, in this study, we demonstrated that frailty is predictive of overall survival after major surgery. Both free T and frailty were independently associated with 1-year mortality. Furthermore, we demonstrated that the addition of free T with a frailty assessment has greater potential to identify surgical patients at higher risks than frailty measures alone. Frail patients with low free T levels have almost a 5-fold increased risk of long-term mortality when compared to nonfrail patients with normal free T. Further multicenter prospective trials should examine the relationship between frailty and low free T to confirm the results.

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Author Contribution

FL drafted the manuscript. FL, GH, SM, and FP completed data acquisition and analysis. FK completed statistical analysis and provided critical revisions of the manuscript. MH, IC, RN, EM, AM, and CR contributed to data analysis and interpretation and provided critical revisions of the manuscript. VAM and KO contributed to conception and design of the study and supervision, and provided critical revisions of the manuscript.

Conflict of Interest

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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Appendix A. Interpretation of laboratory results

Laboratory test	*Reference range*
Free testosterone (1 pg/mL = 3.47 nmol/L)	
Men 18–69 y	35.0–155.0 pg/mL
Men >69 y	30.0–135.0 pg/mL
Total testosterone (1 ng/dL = 0.0347 nmol/L)	
Men	>300 ng/dL
Laboratory test	Reference range for men, 18–150 y old
Creatinine	0.7–1.3 mg/dL
Hemoglobin	12.9–16.1 g/dL
eGFR	≤60 mL/min/1.73 m^2

Appendix B. Fried criteria of frailty for adult men

Weight loss	Unintentional weight loss of ≥10 lb in the last year	
Decreased grip strength	BMI ≤ 24	Grip strength ≤29 kg
	BMI 24.1–26	Grip strength ≤30 kg
	BMI 26.1–28	Grip strength ≤31 kg
	BMI > 28	Grip strength ≤32 kg
Exhaustion	≥2 d of exhaustion in the past week	
Low activity	<1602.47 kJ/wk in the past 2 wk	
Walking speed (10 m)	Height ≤ 173 cm	Walking time ≥ 7 s
	Height > 173 cm	Walking time ≥ 6 s

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